

EDITORIAL COMMENT

Carotid Revascularization Before Open Heart Surgery

The Data-Driven Treatment Strategy*

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Optimal management of high-grade obstructive carotid artery disease at the time of open heart surgery (OHS) has never been addressed in a randomized clinical trial. Data suggest that the combined approach of carotid endarterectomy (CEA) and OHS leads to a higher risk of procedural stroke (1–3), and, therefore, staged carotid revascularization by CEA or carotid artery stenting (CAS) is often performed before OHS. Does the staged approach lead to an overall reduction in the rate of major adverse cardiovascular events (MACE = death, myocardial infarction, and stroke) for patients with concomitant coronary and cerebrovascular disease? The current study reported in this issue of the *Journal* by Shishehbor et al. (4) would suggest that this is true, but only for staged CAS followed by OHS.

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Randomized, controlled trials have demonstrated the superiority of CEA over optimal medical therapy for reducing the future risk of stroke in patients with high-grade carotid artery stenosis (5–8). In patients determined to be at either standard or high risk of perioperative complications during CEA, randomized trials have also shown the non-inferiority of CAS versus CEA in reducing the risk of future MACE (9–11). However, there has been criticism leveled at these data meticulously acquired over the past 2 decades. First, optimal medical therapy has evolved since the completion of the pivotal randomized trials comparing medical therapy with CEA. It has been posited that if such trials were performed today with contemporary antiplatelet, lipid-lowering, and antihypertensive therapy, the benefits of CEA over medical therapy (9% to 15% vs. 22% to 27% ipsilateral

stroke in symptomatic patients at 2 to 3 years [6,7,12,13] and 5% to 6% vs. 11% to 12% death/stroke in asymptomatic patients at 5 years [5,8]) might not be as compelling, especially in asymptomatic patients. However, as all the patients in the current study required OHS, they were at a higher risk of stroke than the patients in the medical therapy versus CEA trials. Second, in the CAS versus CEA trials, myocardial infarction was included as an endpoint. Cumulative data show that the 30-day risk of myocardial infarction is higher with CEA, whereas the risk of minor, nondebilitating cerebrovascular accidents is higher with CAS (11). Major stroke rates at short and longer term follow-up are comparable with both strategies (10,11). Numerous registries limited to patients at high surgical risk during CEA also support an acceptably low rate of MACE after CAS for both symptomatic and asymptomatic patients (14–16). Importantly, the adverse prognosis after perioperative myocardial infarction for noncardiac and vascular surgery is well recognized and of great relevance in discussing the optimal treatment of obstructive carotid disease (17,18).

The study by Shishehbor et al. (4) is unique in that it addresses a cohort of patients with a single high-risk feature during carotid revascularization (i.e., pre-OHS). This is a retrospective analysis of 350 patients treated at the Cleveland Clinic from 1997 to 2009 who presented with combined high-grade coronary and carotid artery disease and met indications for revascularization of both vascular territories. The majority of patients (81%) had asymptomatic carotid disease (the absence of an ipsilateral transient ischemic attack or stroke in the previous 6 months) and underwent coronary artery bypass graft surgery with/without concomitant valve surgery (92%). The study cohort was divided into 3 groups: combined CEA-OHS (n = 195), staged CEA followed by OHS (n = 45), and staged CAS followed by OHS (n = 110). Staged CEA was shortly followed by OHS (median interval, 14 days), whereas a 3- to 4-week interval of dual antiplatelet therapy was usually completed before OHS in the staged CAS-OHS group (median interval, 47 days).

Using all-cause mortality, stroke, and myocardial infarction as a combined primary endpoint, the results of the study show that staged CAS followed by OHS results in a lower risk of MACE compared with the staged CEA-OHS approach (adjusted hazard ratio [HR]: 0.49, 95% confidence interval [CI]: 0.24 to 1.0; p = 0.06) and similar risk of MACE compared with the combined CEA-OHS approach (adjusted HR: 0.99, 95% CI: 0.61 to 1.62; p = 0.97) at the early (1 year) hazard phase. Mortality rates were comparable in all 3 treatment strategies in the early hazard phase, whereas a higher stroke rate was observed in the combined CEA-OHS group and a higher myocardial infarction rate in the staged CEA-OHS group. The late hazard phase (beyond 1 year) favored the staged CAS-OHS group (adjusted HR: 0.33, 95% CI: 0.15 to 0.77; p = 0.01 compared with staged CEA-OHS and HR: 0.35, 95% CI: 0.18 to 0.70; p = 0.003 compared with combined CEA-OHS groups). This late

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difference was primarily driven by higher all-cause mortality in the staged and combined CEA groups beyond 1 year after the index OHS.

The investigators of the current study performed 3 very important analyses to strengthen their reported findings. They derived a propensity score and performed a baseline risk-adjusted comparison of the 3 groups for the composite endpoint and mortality. This propensity-adjusted model was confirmed by performing a propensity-matched analysis in a large subgroup. Second, they provided a median follow-up of 3.7 years, extending the results of their findings beyond the perioperative period. Third, they systematically analyzed each individual patient included in the analysis to capture all adverse clinical events during the follow-up period including all intertreatment events as a part of their MACE endpoint.

Although a propensity-adjusted analysis was performed to account for the baseline differences between the 3 groups, nearly universal neurological monitoring of CAS patients during the time frame of this study likely resulted in a bias favoring CEA with respect to stroke as an endpoint. Additionally, embolic protection devices were only used in 82% of the CAS procedures in this study. Nevertheless, the staged CAS-OHS group had a similar 30-day stroke rate compared with the staged CEA-OHS group and a lower rate than the combined CEA-OHS group.

Although a recent analysis from the CARE registry revealed similar in-hospital and 30-day MACE rates with either CAS or CEA before urgent open heart surgery (19), the registry did not separate staged CEA and combined CEA-OHS, and longer term follow-up was not available. A smaller previous study suggested that CAS before OHS results in superior outcomes compared with combined CEA-OHS at 30 days (3). However, the study did not include intertreatment events, and the results of the current study refute those findings at the early hazard phase.

The systematic collection of all intertreatment events for each individual patient evaluated is a particular strength of this study. A higher incidence of myocardial infarction was observed in the staged CEA-OHS group, whereas the combined CEA-OHS group had the highest incidence of stroke. These data are consistent with previous studies showing a higher incidence of myocardial infarction after CEA in standard- and high-risk patients (8–10). Notably, even in standard-risk carotid disease patients, increased 4-year mortality associated with carotid revascularization-related myocardial infarction has been reported from CREST (Carotid Revascularization Endarterectomy vs Stenting Trial) (20).

As with most retrospective studies, criticisms of this study include the lack of randomization and inherent treatment bias associated with the 3 strategies. Additionally, the role of adjunctive medical therapy as the sole treatment strategy before OHS was not evaluated. Conceivably, this is also a strength of the study in that it reflects actual practice patterns. As most cardiac surgeons are loathe to proceed with OHS in the

presence of high-grade carotid disease, a 3-way randomized trial with medical therapy as an arm would have enrollment bias (asymptomatic moderate disease patients randomized only). Furthermore, as patients with high-grade carotid disease included in the current study met clinical criteria for carotid revascularization, the question of medical therapy as a long-term treatment strategy for these patients is irrelevant.

This study provides clarity in the management of patients with carotid and coronary disease requiring OHS. For patients presenting with an acute coronary syndrome requiring urgent coronary revascularization in whom waiting 3 to 4 weeks is not safe, combined CEA-OHS is the optimum revascularization strategy, although it is associated with higher neurological ischemic events. However, for patients with a stable or an accelerating anginal syndrome who can wait 3 to 4 weeks to complete dual antiplatelet therapy after carotid stenting, staged CAS followed by OHS leads to superior early and long-term outcomes. Staged CEA followed by OHS is associated with an increased short-term (interstage myocardial infarction) and long-term (mortality) hazard and should be avoided. As the majority of patients in this study were undergoing isolated coronary revascularization during OHS, the data should be interpreted with caution in patients with isolated valvular or concomitant coronary and valvular heart disease requiring OHS.

This leads to the final issue confronted by practicing physicians. Despite a wealth of data acquired over 20 years of careful clinical research, CAS only remains available for symptomatic high-risk patients in the United States. In standard-risk or asymptomatic high-risk patients, enrollment in post-marketing registries is required. As patients requiring carotid revascularization before OHS are recognized as a high-risk cohort, the symptomatic status of the patient should not be a factor for reimbursement in this cohort. The present study suggests that the currently acceptable option of CEA before OHS actually endangers the patient, leading to the highest ischemic event rate, both early and late after OHS. These patients should either undergo combined CEA-OHS or be offered the option of CAS before OHS based on medical criteria, not reimbursement issues.

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